Remarks

Claims 2-10, 16, 17, and 19-23 are pending in this case, and subject to final rejection. By this Amendment, claims 3-7 and 20-22 are amended and new claim 24 is added. Claims 21 and 22 are amended only to correct a clerical error. All of the amendments are supported by the specification and claims as originally filed; no new matter is introduced by this amendment.

Applicants expressly reserve the right to pursue protection of any or all of subject matter removed by the current amendment in a subsequent application. After entry of this amendment, **claims 2-10, 16, 17, and 19-24 are pending** in the application. It is believed that the claims are in condition for allowance in the current case, and such action is requested.

Applicants thank the Examiner for acknowledging that the objection to claims 2 and 16, and the rejections of claims 21 and 22 under 35 U.S.C §112 were overcome in the prior response.

Claim Rejections under 35 U.S.C. §112

Claims 2 and 19 remain rejected under §112, first paragraph, as allegedly failing to comply with the written description requirement for the reasons of record in the Office action mailed October 8, 2004. In particular, it is alleged that there is insufficient written description regarding "genes" isolated by the claimed methods. Applicants traverse this rejection, and ask that it be withdrawn.

Applicants understand that the Office is alleging that the specification does not provide sufficient written description for the genes/sequences that are being identified by the screening method of claim 20. The Office appears to be requiring the same level of written description as would be required if Applicants were claiming the genes themselves. This is not, and cannot be, the appropriate standard, as it would make it impossible for any Applicant to ever provide sufficient written description for any screening claim.

In support of this rejection, the Office states that a "method is not described if products used in the method are not described" (action at page 4), and then cites "64 Fed. Reg. 71427, 71428 (1999), comment No. 4." Applicants have obtained and reviewed this document (entitled "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written

Description" Requirement; Request for Comments"; hereinafter "the Interim Guidelines"), and in particular have closely read Comment 4 at page 71428. Applicants cannot see how Comment 4 supports the statement that a "method is not described if products used in the method are not described". If the Office in fact can support this rejection with some portion of the Interim Guidelines themselves (rather than the preliminary Comment), or even a section of the MPEP that has now incorporated the Guidelines, Applicants request that such a citation be provided in the next action.

Applicants note that the language of claim 2 that is rejected (*i.e.*, "preparing a separate heterologous gene construct for each isolated gene") remains unchanged and is identical to that originally filed. The Guidelines (*e.g.*, at page 71434, Part I. in the section entitled "(A) Original Claims") and corresponding MPEP §2163 indicate that written description is usually adequate for language that is present in a claim when the application is filed. With regard to claim 2, therefore, the written description is adequate and the rejection should be withdrawn.

The Office action at page 3 discusses *Amgen Inc. v. Chugai Pharmaceutical Co.* (18 USPQ 2d, 1016 (Fed.Cir. 1991), and MPEP §2163, both for the following:

> "a claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

This passage, however, refers to products – and the rejected claims are method claims, rather than product claims. Applicant is not claiming all of the individual genes/sequences that have been or can be discovered using Applicants' method. The rejection is therefore inappropriately made against the method claims.

Finally, the Office alleges that the methods of claim 2 and 19 require a product (presumably the "each isolated gene" of claim 2 section (vi)), and that product is not adequately described by Applicants. Applicants have provided a sufficient written description for this aspect of the invention, since what is required is adequate written description rather than a recitation of each and every possible species within a genus. In the current instance, Applicants have provided complete and adequate

description of "a method of identifying genes associated with a desired trait in a tomato plant" – as evidenced by the Office not rejecting claim 20 along with claims 2 and 19. Having adequately described how to identify, isolate, and characterize "genes the transcription of which was enhanced by said enhancer" using that method (as is accomplished in claim 20), it cannot be possible that those genes are not adequately described for a claim depending therefrom (*e.g.*, claims 2 and 19).

As acknowledged by the Office, Applicants have described representative sequences using the method of claim 20. There is no expectation whatsoever that other sequences identified by Applicants' claimed method will bear any sequence (structural) similarity to the described sequences – nor should there be. However, that does not in any way undermine the fact that Applicants have provided sufficient written description for the screening methods claimed. Applicants respectfully request that this rejection of claims 2 and 19 be withdrawn.

Claim Rejections under 35 U.S.C. §102(b)

Claims 8, 9, 10, 17, and 20 remain rejected as allegedly anticipated by Jones *et al.* (1994) taken with the evidence of Jones *et al.* (1992) for the reasons of record in the Office actions mailed October 8, 2004 and July 3, 2002. Applicants traverse this rejection, and request that it be withdrawn.

For a claim to be anticipated under §102, the cited reference must disclose each and every element of the claimed invention. Jones *et al.* (1994), even taken with Jones *et al.* (1992), (henceforth referred to collectively as "Jones *et al.*") does not include each and every element of the invention of claim 20, and therefore cannot anticipate the claim (or any claims depending therefrom). In particular, nothing about Jones *et al.* provides an "enhancer" which is a portion of the entire transformation vector and which enhances transcription of gene(s) on the chromosome into which the vector has integrated.

Jones *et al.* is cited for allegedly teaching a tomato transformation system used to isolate the Cf-9 gene based on its transcription having been "enhanced" (page 6 of the July 3, 2002 Office action). To support this statement, the Office references Figure 2 at page 790 of Jones *et al.* (1994). Applicants have carefully reviewed that manuscript, including Figure 2, and can find no teaching of enhanced transcription of Cf-9. Instead, the authors isolated as many as 37 instances of their *Ds* construct inserting into – and thereby disrupting the function of – a "3-kb region of the tomato genome (Fig. 2)…" which they then characterize as encoding Cf-9 (Jones *et al.*, 1994; paragraph bridging pages

789-790). For instance, Figure 1(c) shows a "leaflet . . . variegated for necrosis, which is consistent with **restoration** of Cf-9 function…" when the inserted sequences jump back out of the gene, as discussed in the figure legend and accompanying text (emphasis added). The mutants in Cf-9 were isolated because of loss of function (disruption) of the gene; there is no enhanced transcription discussed, of Cf-9 or any other gene. The maize transposon Activator (Ac) used by Jones *et al.*, and "activation" of transposon elements as discussed in that paper (see, *e.g.*, top of the right-hand column on page 789), cannot and does not substitute for an enhancer element such as Applicants employ in the subject claims.

The Office further alleges, and maintains in the current action, that the term "enhancer" is subjective. Applicants strenuously traverse this assertion, at least as the term is used in the claims and in the context of Applicants' specification. As used in the current context, and as would clearly have been understood by one of ordinary skill at the time the application was filed, the term "enhancer" has a well-defined meaning within the art of molecular biology, and particularly in the context of transgenic plants. Applicants again draw attention to the Exhibit that was submitted along with the response dated January 2, 2004, showing the following definition of enhancer from Molecular Biology of The Cell, 3rd edition (1999):

> "enhancer
> Regulatory DNA sequence to which gene regulatory proteins bind, influencing the rate of transcription of a structural gene that can be many thousands of base pairs away."

This is not contrary to Applicants' discussion of the terms "enhancer" and "element which functions to enhance gene expression" at the bottom of page 5 of the subject specification. That text also refers to activating transcription of DNA, and notes that "enhancers generally act to effect transcription of genes within 1000 to about 5000 or more bp of the insertion site [of the enhancer element]." (Page 5, lines 41-43). It is clear that Applicants' use of the term "enhancer" is in accordance with the understanding of this term in the art at the time the application was filed.

In addition, Applicants provide several representative examples of art-recognized enhancer elements in the subject specification, including those referred to in claim 3 and other claims. The Office appears to acknowledge the specificity of this usage, for instance at page 8 of the July 3, 2002 Office action (noting that a cited reference does not teach certain of the claimed enhancers). In view of

Applicants' teachings, as well as the recognized meaning of the term "enhancer" in the art at the time the application was filed, this term is not subjective.

Claim 20 (from which each of claims 8, 9, 10, and 17 depend directly or indirectly) is directed to a method the first step of which is "transforming cells of a tomato plant with a plant cell expression vector", which vector contains several specified nucleic acid sequences. Each of the sequences is a different and independent element of the claim. Thus, the vector of claim 20 includes "an *E. coli* origin of replication", "an enhancer", "a selectable marker-encoding nucleotide sequence…" and so forth. It is clear from the language of claim 20, and from arguments made previously in prosecution, that the "enhancer" is itself a sequence that is an element of the vector, rather than the entire vector. To further emphasize this, Applicants have herewith amended claim 20 to insert the word "element" after "enhancer", which amendment is supported throughout the specification (*e.g.*, page 3, line 10; page 5, lines 39-42; page 14, line 30; and the original and current claims). It is believed that this amendment does not alter the scope of the claims. Nowhere in Jones *et al.* do the authors teach an element of their transformation vector that is capable, on its own, of enhancing transcription of gene(s) on the chromosome into which the vector has integrated. Without such a teaching, Jones *et al.* does not and cannot anticipate claim 20 (or any of the claims that depend therefrom). Applicants therefore respectfully request withdrawal of this rejection.

Claim Rejections under 35 U.S.C. §103(a)

Claims 2-10, 16, 17, and 19-23 remain rejected as allegedly obvious over Walden *et al.* (1994) in view of Jones *et al.* (1992) for the reasons of record in the Office actions mailed October 8, 2004 and July 3, 2002. Applicants traverse this rejection, and request that it be withdrawn.

In *KSR International Co. v. Teleflex Inc.* 127 S.Ct. 1727 (2007), the Supreme Court affirmed the requisite inquiry for determining obviousness originally set forth in *Graham v. John Deere Co. of Kansas City* 383 U.S. 1 (1966) and noted that the teaching/suggestion/motivation test subsequently formulated by Court of Customs and Patent Appeals and followed by Court of Appeals for the Federal Circuit provided useful insight in determining obviousness, although the test should not be rigidly applied. To establish a *prima facie* case of obviousness, the Office must establish at least three elements. There must be some clear rationale, found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings and/or modify

the teachings reach Applicants' invention. The reference(s) must further provide a reasonable expectation of success that the combination so suggested would be achieved. Finally, the reference(s) must teach or suggest all the claim limitations.

The Patent and Trademark Office (PTO) bears the burden of initially establishing a *prima facie* case of obviousness. MPEP § 2142. Applicant submits that the Office has not met its burden in the instant case.

The Office cites Walden *et al.* (1994) for allegedly teaching a method of identifying and isolating genes implicated in playing a role in plant growth and development in tobacco, the method comprising transforming plant cells with a plant expression vector sharing certain characteristics with Applicants vector. The Office admits this reference does not teach any method in a fleshy fruit-bearing plant (such as tomato), nor several other limitations of Applicants' various claims (*e.g.*, specific enhancers, an herbicide resistance gene, a dwarf plant). Applicants note there are other deficiencies of Walden *et al.*, to be addressed below.

The Office cites Jones *et al.* (1992) as disclosing a method of identifying and isolating genes that play a role in tomato plant growth using transposon tagging. The Office does not suggest the Jones method (or the vector used therein) is the same as the Walden method (or vector), and Applicants would point out that they are not. As discussed more fully below, differences between the Jones and Walden methods, and their respective vectors, undermine any possible expectation that there would be any success in combining the teachings of these references.

Rationale for Combining/Modifying the References

In 2007, the Office recently issued Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc. (72 Fed.Reg. 57526). Provided therein, at page 57529, is a list of example "Rationales" that may be used to support a legal conclusion of obviousness. These include:

(A) Combining prior art elements according to known methods to yield predicable results;
(B) Simple substitution of one known element for another to obtain predictable results;
(C) Use of known techniques to improve a similar device/method/product in the same way;
(D) Applying a known technique to a known device/method/product ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Variation of known work in same or a different field, motivated by design incentives or market forces if the variations would have been predictable to one of ordinary skill in the art; and

(G) A teaching, suggestion, or motivation in the references that would have led one to combine the teachings to predictably arrive at the claimed invention.

In the current case, none of these rationales apply. In view of the following arguments, the rejection of the claims under §103 must and should be withdrawn.

References must teach all Claim Limitations

All of the rationales that may be brought forth to support an allegation of obviousness require first that all of the elements of the claims are present in the reference(s) cited. In the current instance, this is not the case. Even if one were to assume that Walden *et al.* teaches a plant transformation vector that encompasses all elements of Applicants' vector (part (i) of claim 20), neither Walden *et al.*, Jones *et al.*, or a combination of these two references includes all of the method steps required by that claim.

Walden *et al.* teaches selection of cells for growth due to activation of a gene, which activation is alleged to be because of the integration of their "promoter activation tagging" vector. See, for instance, page 1523, Col. 2 of Walden *et al.*, where the authors discuss transforming tobacco protoplasts with agrobacteria containing the activation gene tag, then **selecting** for growth of transgenic cells in the absence of auxin in culture media. The same type of cell-based **selection** system is employed in their screen for cytokinin independent mutants (see page 1524) and mutants modified in polyamine metabolism (also on page 1524).

Thus, Walden teaches exclusively a directed screen that will, at best, only result in the identification of transformed plant cells (*in vitro*) that have a desired characteristic that is pre-selected prior to the start of the screen. Their described method will miss any and all insertional events that implicate a phenotype other than the one they are specifically selecting for (that is, they teach only focusing on a single "desired trait" at a time, to the exclusion of all others), as well as any and all insertional events the effects of which can only be perceived in a whole plant or plant tissue. There is no teaching whatsoever of a method of "selecting **plants** having a desired trait" which trait is caused by transcriptional enhancement mediated by the "enhancer" in the plant transformation vector – as

required by Applicants' claims. Since Jones *et al.* does not teach any method that is capable of identifying a trait that is caused by such transcriptional enhancement (since Jones *et al.* does not teach use of an enhancer element in a transformation vector), neither of the cited references alone or in combination teach this element of Applicants' claimed invention.

It is true that Applicants' claimed method includes "selecting plant cells which have been transformed by their ability to grow in the presence of an amount of selective agent that is toxic to non-transformed plant cells." This, however, is distinct from the "selecting" that yields eventual identification of the "desired trait".

The steps of "regenerating transformed plant cells [that were selected using the "selective agent that is toxic to non-transformed plant cells"] to yield mature plants" and then "selecting plants having a desired trait…" are explicitly recited in the claims. These steps are not provided by either of the cited references, nor would they be considered by one of ordinary skill in the art as obvious extensions of the teachings of the references. For this reason alone, the rejection under §103 cannot and should not be maintained.

Predictability and Reasonable Expectation of Success

Applicants continue to assert that a skilled artisan would not reasonably expect that combining the disclosures of Walden *et al.* and Jones *et al.*, as suggested by the Office, would be successful. The field of screening for and identification of mutants, and more particularly mutant identification based on overexpression of a gene in a plant, is highly unpredictable. This unpredictability undermines each and every one of the possible rationales that the Office might use to support the allegation of obviousness.

One source of the unpredictability and failure of an expectation of success is the admission by Walden *et al.* (by withdrawing various publications related to the work discussed in the cited reference) that their own results with activation tagging in this area were unreliable. The Office insists that Walden *et al.* met with "success . . . in identifying genes associates with a desired trait in tobacco using promoter activation tagging" (see, *e.g.* page 9, July 3, 2002 Office action). However, the subsequent withdrawal of the publications related to the "function of the identified gene" (page 5, October 8, 2004 Office action) in fact indicates that Walden *et al.* had not met with any success in

identifying a desired gene using promoter activation tagging. At best, Walden *et al.* teaches that they can make a vector and can recover a sequence from the genome of a plant cell adjacent to the integrated vector. Because their results (the function of the gene identified) were withdrawn, Walden *et al.* in fact did not meet with any "success" in using a method even remotely similar to Applicants' claimed method.

Given that the teaching of Walden *et al.* must be viewed as only being applicable to selecting traits that are limited to *in vitro* plant cells, it is also important to note that the art recognized (contemporaneous with Applicants' filing) that effects *in vitro* were not always predictive of results *in vivo* with plants. For instance, Li *et al.* (1999) describes a system of native gene activation in *Phaseolus vulgaris* (based on chromatin architecture) that has clearly different effects in whole plants than in *in vitro* cell culture. This is illustrative of only one of myriad other effects that were recognized as being dependent on the context of expression in a whole organ/organism. In view of these recognized differences between *in vitro* gene expression and whole plant/*in vivo* expression, one of ordinary skill would not have had a reasonable expectation of success in translating the cell-culture based methods of Walden *et al.* into a whole plant system. (Notably, Walden *et al.* was not able to make this translation.)

More generally, contemporaneous with Applicants' filing, it was well recognized in the field that overexpression of genes in plants, including in the context of transgene expression, was fraught with unexplained and difficult issues. These included, for instance, various epigenetic effects, post transcriptional gene silencing (PTGS), paramutation effects, co-suppression, and so forth. See, for instance, Napoli *et al.* (1990) – describing co-suppression; Brigneti *et al.* (1998) – describing transgene silencing; Jakowitsch *et al.* (1999) – describing silencing and methylation of homologous promoters in *trans*; and Mette *et al.* (2000) – describing transcriptional silencing. Gene silencing is also reviewed, for instance, in Matzke *et al.* (2001) and Maine (2000). In view of the unpredictability of the field of expression in plants at the time, one of ordinary skill would not have reasonably expected to meet with success in using the Walden *et al.* method/vector – which at best had been demonstrated to be only partially successful and that only in cell limited plant culture – in the Jones *et al.* plant system.

Given the failure of Walden *et al.* to actually identify or characterize a gene using their "promoter activation tagging" system in tobacco cell culture, as well as the general unpredictability of

systems used for expressing (and particularly overexpressing) genes in plants, a skilled artisan would not reasonably expect that a vector similar to that of Walden *et al.* could be used successfully and with predictable outcome when applied to a plant mutation screening system such as used by Jones *et al.*.

This discussion clearly demonstrates that the art was unpredictable and thus the skilled artisan working at the time of the invention would have no reasonable expectation that the combination suggested by the Office would be successful. In view of the foregoing, reconsideration and withdrawal of the claim rejections under §103 are respectfully requested.

New Claim

Applicants have added new claim 24, which is supported by the application and claims as originally filed. This claim is added to explicitly note that, in the claimed embodiment, the "desired trait" is different from the trait used to select the transformed plant cells ("ability to grow in the presence of an amount of selective agent that is toxic to non-transformed plant cells"). This method is clearly distinguishable from all of the references of record, and is believed to be allowable as written.

Conclusion

Applicants respectfully submit that the claims submitted herewith are in condition for allowance. If any issues impede the issuance of a notice of allowance, the Examiner is requested to contact the undersigned prior to the mailing of an Advisory action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance of the claims.

Respectfully submitted,

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